COMMENTARY

Risk of fatal pulmonary embolism with oral contraceptives

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A case-report of a pulmonary embolism (PE) associated with taking oral contraceptives (OCs) was published shortly after they were introduced into clinical practice in 1960.[1] Thereafter, a series of case-control studies supported by limited cohort-study data have been consistent in showing that use of combined OCs is associated with a variable but clearly increased risk of venous thromboembolic events (VTE)—either deep-vein thromboses, PEs, or a mixture.[2]

The report in today's *Lancet* by L Parkin and colleagues from New Zealand on fatal PE and OCs makes an important addition to current knowledge, largely because most of the evidence hitherto has related to non-fatal VTEs. One case-control study of 26 cases of fatal idiopathic VTE (ie, not associated, for example, with recent surgery, trauma, or pregnancy) published in 1968[3] found an odds ratio associated with current OC use of 8—similar to the 9·6-fold increase reported in this, more contemporary, New Zealand study. This similarity reinforces the observation that the level of OC-associated risk of VTE does not seem to have fallen with the use of products containing lower doses of oestrogen than in the past.[4]

The New Zealand report may be criticised for use of unconditional unmatched analyses despite a matched design for the study. However, given the small numbers of women involved in this study, this option is probably the correct one. The definition of current OC use—prescribed use at any time during the 3 months before the index date—may be criticised because most data suggest that the risk of VTE has largely disappeared by about 6 weeks after stopping OC use. Nevertheless, most OC prescriptions are for at least 3 months, and although it cannot be proven that these OCs were taken up to the time of the index event, the definition of current user seems reasonable and unlikely to produce a spuriously increased risk estimate.

A third potential criticism of the New Zealand study is the adjustment of data for weight rather than body-mass index (BMI), which is one of the few acquired risk factors for VTE reasonably established among largely idiopathic cases. However, the impact of adjustment for BMI rather than weight is likely to be minimal.

This new study confirms that death from PE is rare among OC users. Two-thirds of PE deaths occurred in OC users, but the estimated absolute risk of fatal PE in current OC users was 10·5 per million women-years. Although this risk is low, the investigators point out that it is higher than might be expected from previously reported incidence and case-fatality rates for VTE. However, it may be that reported case-fatality rates for young women who are otherwise healthy are inaccurate. What is clear from these data is the finding that OCs containing desogestrel or gestodene are associated with higher risks of fatal PE than are those containing levonorgestrel. This finding is consistent with most previous studies comparing the effects of second-generation with those of third-generation progestagens on VTE.[5] The possibility that these differences can be explained away by various biases and confounding seems most unlikely,[6] and the only real debate is what the size of the effect is (somewhere between a 50% and 100% increase seems reasonable) and what its underlying mechanism might be.

It is surprising that third-generation OCs are used extensively in New Zealand, since the regulatory authorities there have been conservative in their acceptance of other pharmacological agents, such as angiotensin II antagonists, presumably on the bases of lack of proven benefits and cost.

Although the absolute risk of fatal PE due to OCs is very small, and much less than that associated with pregnancy, the link between PE and combined OC use is clearly of clinical importance, not least because the diagnosis is easily missed and because the complication is a side-effect of a drug prescribed by the medical profession for young healthy women. To cause an increase (possibly a doubling) of the risk of fatal PE, however small, is unnecessary. Hence, these data support previous pragmatic recommendations that second-generation pills (those containing levonorgestrel) are the combined OC of first choice.[7]

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